

From the INTERNATIONAL BUREAU

**PCT**NOTIFICATION CONCERNING  
TRANSMITTAL OF COPY OF INTERNATIONAL  
PRELIMINARY REPORT ON PATENTABILITY  
(CHAPTER I OF THE PATENT COOPERATION  
TREATY)

(PCT Rule 44bis.1(c))

To:

MALLON, Joseph, J.  
Knobbe Martens Olson & Bear LLP  
2040 Main Street  
14th Floor  
Irvine, CA 92614  
ETATS-UNIS D'AMERIQUE

Date of mailing ( <i>day/month/year</i> ) 19 November 2009 (19.11.2009)		
Applicant's or agent's file reference NEREUS.160VP		IMPORTANT NOTICE
International application No. PCT/US2008/062553	International filing date ( <i>day/month/year</i> ) 02 May 2008 (02.05.2008)	
		Priority date ( <i>day/month/year</i> ) 04 May 2007 (04.05.2007)
Applicant NEREUS PHARMACEUTICALS, INC. et al		

The International Bureau transmits herewith a copy of the international preliminary report on patentability (Chapter I of the Patent Cooperation Treaty)

The International Bureau of WIPO  
34, chemin des Colombettes  
1211 Geneva 20, Switzerland

Authorized officer

Yoshiko Kuwahara

Facsimile No. +41 22 338 82 70

e-mail: [pt07.pct@wipo.int](mailto:pt07.pct@wipo.int)

## PATENT COOPERATION TREATY

## PCT

## INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44bis)

Applicant's or agent's file reference NEREUS.160VP	<b>FOR FURTHER ACTION</b>		See item 4 below
International application No. PCT/US2008/062553	International filing date ( <i>day/month/year</i> ) 02 May 2008 (02.05.2008)	Priority date ( <i>day/month/year</i> ) 04 May 2007 (04.05.2007)	
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237			
Applicant NEREUS PHARMACEUTICALS, INC.			

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 bis.1(a).

2. This REPORT consists of a total of 12 sheets, including this cover sheet.

In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

- |  |   |
|--|---|
| <input checked="" type="checkbox"/> Box No. I    | Basis of the report   |
| <input type="checkbox"/> Box No. II              | Priority  |
| <input checked="" type="checkbox"/> Box No. III  | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability  |
| <input type="checkbox"/> Box No. IV              | Lack of unity of invention  |
| <input checked="" type="checkbox"/> Box No. V    | Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| <input checked="" type="checkbox"/> Box No. VI   | Certain documents cited   |
| <input type="checkbox"/> Box No. VII             | Certain defects in the international application  |
| <input checked="" type="checkbox"/> Box No. VIII | Certain observations on the international application   |

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44bis.3(c) and 93bis.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44bis.2).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland  Facsimile No. +41 22 338 82 70	Date of issuance of this report 10 November 2009 (10.11.2009)
	Authorized officer  Yoshiko Kuwahara  e-mail: p07.pct@wipo.int

# PATENT COOPERATION TREATY

From the  
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

# PCT

## WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing  
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference  
see form PCT/ISA/220

**FOR FURTHER ACTION**  
See paragraph 2 below

International application No.  
PCT/JS2008/062553

International filing date (day/month/year)  
02.05.2008

Priority date (day/month/year)  
04.05.2007

International Patent Classification (IPC) or both national classification and IPC

INV. A61K31/133 A61K31/407 A61K31/4409 A61K31/4965 A61K31/65 A61K31/7036 A61K38/06 A61K45/06  
A61P31/00 A61P31/16 A61P31/08 A61P11/00 A61P27/16 A61P1/12 A61P31/06 A61P13/02 A61P31/04

Applicant  
NEREUS PHARMACEUTICALS, INC.

**1. This opinion contains indications relating to the following items:**

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

**2. FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1b(c) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

**3. For further details, see notes to Form PCT/ISA/220.**

Name and mailing address of the ISA:



European Patent Office - P.B. 5818 Patents  
NL-2280 HV Rijswijk - Pays Bas  
Tel. +31 70 340 - 2040 Tx: 31 651 epo nl  
Fax: +31 70 340 - 3016

Date of completion of  
this opinion

see form  
PCT/ISA/210

Authorized Officer

Cielen, Elsie

Telephone No. +31 70 340-4540



**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**

International application No.  
PCT/US2008/062553

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**Box No. I Basis of the opinion**

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1. With regard to the **language**, this opinion has been established on the basis of:
  - ☒ the international application in the language in which it was filed
  - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).
2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))
3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
  - a. type of material:
    - ☐ a sequence listing
    - ☐ table(s) related to the sequence listing
  - b. format of material:
    - ☐ on paper
    - ☐ in electronic form
  - c. time of filing/furnishing:
    - ☐ contained in the international application as filed.
    - ☐ filed together with the international application in electronic form.
    - ☐ furnished subsequently to this Authority for the purposes of search.
4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
5. Additional comments:

**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**

International application No.  
PCT/US2008/062553

**Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

- ☐ the entire international application
- ☒ claims Nos. 1-5, 7-14, 16-18 (all partially)

because:

- ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international search (*specify*):
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):
- ☒ no international search report has been established for the whole application or for said claims Nos. 1-5, 7-14, 16-18 (all partially)
- ☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:
- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13ter.1(a) or (b).
- ☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-bis of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.
- ☐ See Supplemental Box for further details

**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**

International application No.  
PCT/US2008/062553

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**Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

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**1. Statement**

Novelty (N)	Yes: Claims	<u>4, 5, 8, 13, 14, 17</u>
	No: Claims	<u>1-3, 6, 7, 9-12, 15, 16, 18</u>
Inventive step (IS)	Yes: Claims	<u>-</u>
	No: Claims	<u>1-18</u>
Industrial applicability (IA)	Yes: Claims	<u>1-18</u>
	No: Claims	

**2. Citations and explanations**

see separate sheet

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**Box No. VI Certain documents cited**

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**1. Certain published documents (Rules 43bis.1 and 70.10)**

and / or

**2. Non-written disclosures (Rules 43bis.1 and 70.9)**

see form 210

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**Box No. VIII Certain observations on the international application**

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The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

**Re Item III**

**Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

**III.i.** This application does not meet the requirements of Article 5 and 6 PCT, because claims 1-5, 7-14 and 16-18 are not clear, nor sufficiently supported and the invention is not sufficiently disclosed by the description.

(a) Present claims 1-5, 7-14 and 16-18 relate to a very large number of possible compounds. Support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds of claims 6 and 15, and to formulae I and II wherein E1 and E3 are both O, which is a generalisation of all the exemplified compounds.

(b) Moreover, present claims 1-5, 7-14 and 16-18 relate to compounds which actually are not well-defined. The use of the definition "pro-drug thereof" in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. The lack of clarity is such as to render a meaningful complete search impossible. Consequently, the search has been restricted to the compounds as specified under item III.i(a).

**III.ii.** No opinion will be given in respect of subject-matter which is not covered by the search report (Rule 66.1(e) PCT) (see also item V.I).

**Re Item V**

**Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

**V.i.(a)** Attention is drawn to the fact that the present statement expressed as to novelty, inventive step and industrial applicability refers only to matter for which an International

Search Report has been drawn up (see item III).

(b) Present claims 1-9 relate to a method of treatment. The patentability can be dependent upon the formulation of the claims. The EPO, for example, does not recognise as patentable claims to the use of a compound in medical treatment, but may allow claims to a product, in particular substances or compositions for use in a first or further medical treatment.

**V.ii. Reference is made to the following documents:**

- D1: WO 2004/071382 A (BAYER HEALTHCARE AG [DE]; STADLER MARC [DE]; SEIP STEPHAN [DE]; MUELLE) 26 August 2004 (2004-08-26)
- D2: WO 2006/060809 A (NEREUS PHARMACEUTICALS INC [US]; PALLADINO MICHAEL [US]; POTTS BARBARA) 8 June 2006 (2006-06-08)
- D3: M. O'NEIL: "The Merck Index Thirteenth Edition" 2001, MERCK RESEARCH LABORATORIES, WHITEHOUSE STATION N.J., XP002510887
- D4: M.H. BEERS, R. BERKOW: "The Merck Manual of Diagnosis and Therapy" 1999, MERCK RESEARCH LABORATORIES, WHITEHOUSE STATION N.J., XP002510943
- D5: US 2004/138196 A1 (FENICAL WILLIAM [US] ET AL FENICAL WILLIAM [US] ET AL) 15 July 2004 (2004-07-15)
- D6: WO 2005/094423 A (HARVARD COLLEGE [US]; GOLDBERG ALFRED L [US]) 13 October 2005 (2005-10-13)
- D7: US 2005/203029 A1 (SCHUBERT ULRICH [DE] ET AL) 15 September 2005 (2005-09-15)
- D8: SCHIEWE H (REPRINT) HAUSTEDT L O ET AL: "Rational approaches to natural-product-based drug design" CURRENT OPINION IN DRUG DISCOVERY & DEVELOPMENT, (JUL 2006) VOL 9, NO. 4, PP. 445-462. ISSN: 1367-6733. PB - THOMSON SCIENTIFIC, MIDDLESEX HOUSE, 34-42 CLEVELAND STREET, LONDON, W1T 4JE, ENGLAND., July 2006 (2006-07), XP008100461
- D9: NICOLAUS B J R: "Symbiotic Approach to Drug Design" DECISION MAKING IN DRUG RESEARCH, XX, XX, 1 January 1983 (1983-01-01), pages 173-186, XP002197412

**V.iii. Article 33(2) PCT.**

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-3, 6, 7, 9-12, 15, 16 and 18 is not new in the sense of Article 33(2) PCT.

(a) Document D1 discloses that compounds which fit in present formula I are proteasome inhibitors (p. 3, par. 4 - p. 4, par. 3; p. 6, par. 4 - p. 8, par. 1; examples 1-3; p. 56, par. 4 - last par.; p. 57, table A; claims 1-3). They can be used for the treatment of fungal, viral and bacterial infections, alone or in combination with other active compounds, and for the treatment of *inter alia* toxic shock syndrome, sepsis, cerebral malaria, tuberculosis and fever (p. 19, last par. - p. 20, par. 2). Therefore, the subject-matter of present claims 1-3, 7, 9-12, 16 and 18 is not novel over D1.

(b) Document D2 discloses the use of the presently claimed compounds, including Salinosporamide A, for the treatment of *inter alia* septic shock, trachoma, and infectious diseases, including Plasmodium and Trypanosoma (par. [0013]-[0021], [0126], [0170], [0198]-[0203], [0218]-[0220], [0313], [0320]; claims 23, 33, 34, 41, 49, 51, 52). Plasmodium is generally known to cause malaria. Optionally, other antimicrobial agents can be coadministered (par. [0293]). The compounds are proteasome inhibitors (par. [0272], [0274]; examples 36, 40, 51, 60, 61; par. [0538]). Therefore, the subject-matter of present claims 1, 6, 7, 9, 10, 15, 16 and 18 is not novel over D2.

**V.iv. Article 33(3) PCT.**

(a) The problem to be solved by the present application is the provision of alternative medicines for the treatment of specific infectious diseases, preferably tuberculosis.

The proposed solution is the use of [3.2.0] heterocyclic compounds of formulae (I) or (II), preferably salinosporamide A.

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-18 - as far as novel - does not involve an inventive step in the sense of Article 33(3) PCT.

(b) As far as the treatment of tuberculosis is concerned, document D1 can be considered

to represent the closest state of the art (see item V.II(a)).

(i) The subject-matter of present claims 4-5 and 13-14 differs herefrom in that the mycobacteria causing tuberculosis are specified.

This subject-matter does not involve an inventive step, because from D4 it is known that tuberculosis is caused by *Mycobacterium tuberculosis*, *M. bovis* or *M. africanum* (p. 1193, right-hand column, par. 1).

(ii) The subject-matter of present claims 6 and 15 differs herefrom in that Salinosporamide A, which has as R<sub>1</sub> an alkyl chain of different length and substituted by Cl, is used.

The problem to be solved may therefore be regarded as the provision of an alternative proteasome inhibitor for the treatment of the same disease.

The solution proposed in claims 6 and 15 does not involve an inventive step, because the compounds of D1 are disclosed as alternatives to Salinosporamide A (D1: p. 3, last par. - p. 4, par. 1). Moreover, structure-activity relationship investigation of the R<sub>1</sub> side chain has demonstrated that compounds having a good leaving group in the R<sub>1</sub> side chain (as in Salinosporamide A) have increased activity (see D2, example 60, in particular par. [0528]-[0531]).

It was therefore obvious for the skilled person, knowing from D1 that proteasome inhibitors structurally very close to Salinosporamide A can be used for the treatment of tuberculosis and from D2 that compounds having a good leaving group in the R<sub>1</sub> side chain have increased activity, to at least try to use Salinosporamide A for the treatment of tuberculosis with a reasonable expectation of success.

In the absence of comparative data and/or convincing arguments showing a surprising and/or unexpected effect linked to the use of Salinosporamide A instead of the compounds of D1 for the treatment of tuberculosis, an inventive step cannot be recognised at present.

(iii) The subject-matter of present claims 8 and 17 differs from D1 in that specific anti-infective agents are coadministered. This subject-matter does not involve an inventive step because from D3 it is known that these compounds are antibacterial or even tuberculostatic agents (p. THER-5, column 3 - p. THER-7, column 2).

(c) Furthermore, even if novelty could be restored, the present application would very likely lack an inventive step over D2, which clearly teaches the use of compounds of formulae I and II, including Salinosporamide A, for several of the presently claimed infectious diseases, optionally in combination with further antimicrobial agents (see item V.II(b)).

(d) The present application also lacks an inventive step over each of D6-D7.

Document D6 discloses the treatment of bacterial infections, such as *Mycobacterium tuberculosis*, *Mycobacterium leprae*, *Clostridium perfringens*, *Listeria monocytogenes*, *Staphylococcus aureus*, *Staphylococcus epiderm*, *Streptococcus mutans*, *Streptococcus pneumoniae*, *Brucella*, *Campylobacter*, *Escherichia coli*, *Gardnerella vaginalis*, *Haemophilus influenzae*, *Helicobacter pylori*, *Salmonella enteridis*, *Salmonella typhi*, *Shigella boydii*, *Streptococcus pyogenes*, *Yersinia enterocolitica*, *Yersinia pestis*, *Chlamydia psittaci*, *Chlamydia trachomatis*, *Mycoplasma pneumoniae* and *Ehrlichia chafensis*, preferably *Mycobacterium tuberculosis*, with a peptide compound which selectively inhibits bacterial proteasomes (par. [003], [012], [029]-[033]; claims 1, 6-8).

Document D7 teaches that proteasome inhibitors, optionally in combination with other antiviral agents, such as clastolactacystein beta-lactone (=omuralide) or PS-519, are used for the treatment of virus infections by Flaviviridae or Pestivirus, such as diarrheal diseases (par. [0067]-[0068], [0109]; claims 44, 45, 48, 51 and 53).

The subject-matter of present claims 1-18 differs herefrom in that alternative proteasome inhibitors are used.

The problem to be solved may therefore be regarded as the provision of an alternative proteasome inhibitor for the treatment of specific infectious diseases.

The solution proposed in claims 1-18 - as far as novel - does not involve an inventive step, because Salinosporamide A is known to be an exceptionally high and selective inhibitor of proteasomes, more potent than omuralide and PS-519 (see e.g. D8, p. 455, right-hand column, par. 2).

It was therefore obvious for the skilled person, knowing from each of D6 and D7 that proteasome inhibitors can be used for the treatment of the claimed infectious diseases and from e.g. D8 that Salinosporamide A is an exceptionally high and selective inhibitor of proteasomes, to at least try to use Salinosporamide A for the treatment of the claimed infectious diseases with a reasonable expectation of success.

In the absence of comparative data and/or convincing arguments showing a surprising and/or unexpected effect linked to the use of Salinosporamide A instead of the compounds of D6 and D7 for the treatment of the claimed infectious diseases, an inventive step cannot be recognised at present.

(e) Moreover, it appears that the problem underlying the application has not been solved over the whole of the scope of the claims: Document D5 states on p. 3, par. [0051] and in

example 2 that "Salinosporamide A ... shows little antifungal activity against *C. albicans* and no antibacterial activity (*S. aureus*, *E. faecium*)."

In this respect, it is to be noted that the only pharmacological data relate to the treatment of tuberculosis (example 36-37). The latter example contains a mere statement, without any real data. Example 43 relates to antimicrobial assays for a variety of infectious diseases, but does not contain any data.

A positive opinion on inventive step can be given only if and as far as the problem underlying the application actually is solved by all claimed variants.

(f) Claims 1-5, 7-14 and 16-18 of the present application relate to a very wide variety of compounds which all are supposed to be effective in the treatment of the claimed infectious diseases (see also items III.i(a) and VIII).

By virtue of the many possible substituents, which in themselves at least in part will represent further pharmacophoric moieties, it appears to be highly questionable that it is predictable that all claimed variants actually will exhibit the claimed properties in relation to the treatment of the sepcific infectious diseases. The skilled person is aware of the fact that the effects of such hybrid compounds comprising more than one pharmacophoric group cannot be foreseen having regard to the preparation of a medicament for the claimed therapeutic utility (see also D9). The presence of an inventive step can only be recognised for problems which have been solved by all claimed variants.

#### **Re Item VI**

##### **Certain documents cited**

The examination has been carried out assuming that the priority of the application is valid. However, attention is drawn to the fact that the document which has been cited in the search report as "P" document, namely WO2007138116, may become relevant in the national/regional examination phase.

**Re Item VIII**

**Certain observations on the international application**

Claims 1-5, 7-14 and 16-18 of the present application relate to a very wide variety of compounds which all are supposed to be effective in the treatment of a very large number of infectious diseases (see also items III.i(a) and V.iv(f)).

In fact, the number of claimed variants cannot be estimated without undue burden and in any case appears to be fully disproportionate to what actually is disclosed and supported by pharmacological evidence, namely the use of Salinosporamide A for the treatment of tuberculosis (example 36-37). (see also item V.iv(e)).

As a rule, protection conferred by a patent should be commensurate with the range of compounds for which the effect has been properly demonstrated, including obvious variants thereof. Having to construe the numerous variants comprised in claims 1-5, 7-14 and 16-18 and to form an opinion on whether or not any one of them has anti-infective activity against one of the claimed diseases imposes a severe and undue burden on the skilled person. It follows that the present application as it stands falls foul of the clear provisions of Articles 5 and 6 PCT.